

***Remarks***

Claims 45-63 and 82 - 83 are pending. Claim 83 has been amended.

At the outset, Applicants point out it is asserted in the Office Action that claims 45-86 are pending, and that claims 64-81 are duplicative and must be deleted.

In response, Applicants point out that claims 64-81 were canceled in the previous response. Further, Applicants are unclear as to what claims the Examiner is referring in connection with the asserted rejection of claims 84-86, as no such claims were pending at the time the present office action was issued. In the previous response, and as stated above, claims 63-81 were canceled and new claims 82-83 were added.

***Claim Rejections - 35 USC § 103***

The examiner has maintained the rejection of all the claims under 35 USC 103(a) and deemed the claims to be obvious over Jablonka et al., Archivum Veterinarium Polnicum (1992) Vol. 32, pp 57-66, in view of Stoll et al. Annals N.Y. Accad. Sci. (1994), pp 122-128; Biewenga et al. Gen Pharm (1997) Vol. 29, pp 315-331; Sian et al. Annals of Neurology (1994) Vol 35, pp 348-355, and Kozhenivkova et al. Bull. Experimental Biol. and Med. (1999) Vol. 128, pp 535-537.

In maintaining this rejection, the Examiner contends that Applicants' arguments set forth in the previous response have been foreclosed by the case of *KSR v. Teleflex 127 S. Ct. at 1741 (2001)*. It is asserted that the foreclosed arguments are that there must be a motivation to combine the references found in the references, and that the references must teach all of the claim limitations. However, irrespective of KSR, Applicants have also submitted in the last response the important argument that one skilled in the art at the time the present invention was made must have been able to form a reasonable expectation of success in arriving at the present invention. This standard has not been modified by the KSR decision and remains a requirement for a *prima facie* case of obviousness under both the MPEP and the Federal Circuit. Further, it is also still a requirement that a reasonable expectation of success not be based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). In this regard, it is asserted in the Office Action, with the ostensible support of a variety of cases, that a greater than additive effect (i.e., a synergistic effect) that is expected is not patentable,

and that a greater than additive effect in the present case would have been expected. Additionally, the Office Action presents the unsupported assertion that Applicants have failed to provide conclusive evidence for the lack of effect for single agents acting alone (see Office Action page 5, second full paragraph, last three sentences). For at least the following reasons, Applicants strongly disagree.

It is respectfully submitted that no substantive evidence is on the record in support of the Examiner's contention that a greater than additive effect (i.e., a synergistic effect) according to the present claims would have been expected by one skilled in the art at the time the present invention was made. In particular, each of the present claims require ambroxile. It is asserted in the Office Action that Jablonka et al. teach a composition comprising ambroxile for stimulating GSH, and that Sian et al. teach reduced GSH in Parkinson's disease and patients with neurodegenerative disorders. Therefore, the present obviousness rejection is based on the assumption that, from the combination of Jablonka et al. and Sian et al. (and/or the other cited references), one skilled in the art at the time the present application was filed would have had a reasonable expectation that ambroxile alone would exhibit at least some neuroprotective effect. However, there is clear evidence on the record that ambroxile (as well as other claimed agents) has no such effect when used alone. Therefore, if one skilled in the art, upon reading of the alleged GSH stimulatory effects of ambroxile in Jablonka et al., and of reduced GSH in neurodegenerative disorders as in Sian et al., tested ambroxile for neuroprotective effects, he would have observed (as is established in the present record) that ambroxile has no neuroprotective effect. Accordingly, it would be illogical to conclude that this skilled person would thereafter continue to combine agents with allegedly known GSH stimulatory properties to eventually achieve an additive effect because, as should be self-evident, addition of one agent with no effect to another agent with similar functional properties would be expected to result in an additive effect of zero. This reasoning is consistent with the recent guidance provided by the Federal Register (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007), which states in connection with rebutting an obviousness rejection:

“For example, in the case of a claim to a combination, applicants may submit evidence or argument to demonstrate that... the elements in

combination do not merely perform the function that each element performs separately.”

Therefore, Applicants submit it is clear that the present invention is non-obvious over the cited references because the elements in the present combination do not merely perform the same function that each element performs separately, because separately, each element exhibits no neuroprotective effect.

In connection with the foregoing, Applicants submit that there is no support in the Office Action for the assertion that the evidence of record is inconclusive to show the lack of effect of single agents alone. In particular, specific evidence that when used alone, each of the claimed compounds have **no effect** on reduction of neuronal damage was provided in the previously filed response. Applicants thus reiterate that the record clearly demonstrates that the presently claimed agents, when each is provided alone, are not capable of reducing neuronal damage (and again point out page 9, line 21, through page 10, line 4 of the present specification), while the combination of the claimed agents is capable of eliciting a significant and synergistic neuroprotective effect (and again point out the present specification in Example 3, as well as the data appended to the Declaration of Dr. Frank Striggow and submitted with the Applicants’ response of December 12, 2006). In this regard, the Examiner’s attention is courteously drawn to the Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007, which states:

“Once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. All the rejections of record and proposed rejections and their bases should be reviewed to confirm their continued viability. The Office action should clearly communicate the Office’s findings and conclusions, articulating how the conclusions are supported by the findings.”

In view of this, Applicants respectfully request such reconsideration and a clear communication as to how one skilled in the art would have formed a reasonable expectation of the synergistic properties of the present invention from the cited references, and why it is asserted that Applicants have failed to provide conclusive

evidence that when used alone, each of the claimed compounds have no effect on reduction of neuronal damage .

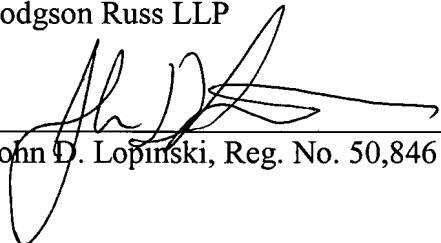
Thus, in summary, Applicants respectfully submit that the multiple assertions in the Office Action that the presently claimed synergistic properties of the instant invention would have been expected by one skilled in the art are unsupported in the record and are plainly incorrect based upon evidence that is actually present in the record. Moreover, Applicants note that *In re Korkhoven* has been cited multiple times in support of the present obviousness rejection. However, one of the reasons the obviousness rejection was upheld in *In re Korkhoven* is because comparative test data offered by the appellant as evidence of the superiority of the claimed method was not commensurate in scope with the claims (see *In re Korkhoven*, at 851). In contrast, the present case provides claims to combinations of agents, an analysis of the effect of the compounds cited in the prior art, and a demonstration that the assumption that each compound alone would be effective for providing a neuroprotective effect is incorrect. Thus, Applicants submit the present invention is clearly patentable over the cited references and the knowledge of one skilled in the art at the time the present application was filed.

### ***Conclusion***

Based on the arguments and amendments presented herein, Applicants believe all the pending claims are now in condition for allowance and respectfully request the Examiner to allow all the claims. A Request for Continued Examination and a check for the required fee is enclosed. Please charge any additional fees due or credit any overpayment to deposit account number 08-2442.

Respectfully submitted,  
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